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(54) Title: PLASMINOGEN ACTIVATOR INHIBITOR ANTAGONISTS RELATED APPLICATIONS

(57) Abstract: Compounds and pharmaceutical compositions useful as plasminogen activator inhibitor (PAI) antagonists are provided. In particular, methods of antagonizing PAI with substituted and unsubstituted aryl and heteroaryl ethers and thioethers, benzils, benzyl ethers, benzoate esters, sulfones and benzophenones are provided.

PLASMINOGEN ACTIVATOR INHIBITOR ANTAGONISTS

RELATED APPLICATIONS

For U.S. purposes and where appropriate, benefit of priority under 35 U.S.C. §119(e) to U.S. provisional application Serial No. 60/185,564, filed February 28, 2000, to Edwin L. Madison, Terence K. Brunck, Joseph Edward Semple, Marguerita Lim-Wilby and Kent E. Pryor, entitled "PLASMINOGEN ACTIVATOR INHIBITOR ANTAGONISTS" is claimed. For U.S. purposes and where appropriate, this application is a continuation-in-part of U.S. application Serial No. 09/580,535, filed May 26, 2000, to Edwin L. Madison, Terence K. Brunck, Joseph Edward Semple, Marguerita Lim-Wilby and Kent E. Pryor, entitled "PLASMINOGEN ACTIVATOR INHIBITOR ANTAGONISTS," and is a continuation-in-part of U.S. application Serial No. 09/444,172, filed November 19, 1999, to Edwin L. Madison, Terence K. Brunck, Joseph Edward Semple, Marguerita Lim-Wilby and Kent E. Pryor, entitled "PLASMINOGEN ACTIVATOR INHIBITOR ANTAGONISTS." Priority is claimed herein to the above-referenced applications.

U.S. application Serial No. 09/580,535 is a continuation-in-part of U.S. application Serial No. 09/444,172 and claims benefit of priority under 35 U.S.C. §119(e) to U.S. provisional application Serial No. 60/185,564.

For U.S. purposes and where appropriate, the disclosures of U.S. application Serial Nos. 09/580,535, 09/444,172 and U.S. provisional application Serial No. 60/185,564 are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Provided herein are compounds and pharmaceutical compositions that are plasminogen activator inhibitor (PAI) antagonists. In particular, methods of antagonizing PAI, particularly plasminogen activator inhibitor

type 1 (PAI-1), with substituted and unsubstituted biaryl and benzyl ethers and thioethers, benzils and benzophenones are provided.

BACKGROUND OF THE INVENTION

Plasminogen activators (PA's), such as tissue type plasminogen activator (tPA) and urokinase plasminogen activator (uPA), are serine proteases that control the activation of the zymogen, plasminogen, to the active enzyme plasmin. Plasmin is important in a number of (patho)-physiological processes, including fibrinolysis, tissue remodelling, tumor growth and metastasis. The glycoprotein PAI-1 is an endogenous fast-acting inhibitor of PA activity. PAI-1 is a member of the serpin (serine protease inhibitor) family of protease inhibitors and is synthesized by a variety of cells including endothelial cells. An imbalance between PAs and PAI-1 contributes to several pathological conditions including thrombosis, inflammation, tumor growth and metastasis.

Thrombosis

Elevated circulating levels of PAI-1 can result in a downregulation of fibrinolysis. This condition can contribute to the pathogenesis of various thrombotic disorders, including myocardial infarction, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation. Compounds and pharmaceutical compositions that antagonize PAI-1 can be used in the treatment of certain thrombotic disorders by enhancing the extent of endogenous fibrinolysis by PAs. In addition, PAI-1 antagonists, in this context, may enhance the efficacy of thrombolytic therapy where exogenous PAs such as recombinant tPA (r-tPA) is administered to a patient to reperfuse blood vessels occluded by thrombus as is commonly observed in myocardial infarction (see, e.g., U.S. Patent Nos. 5,750,530, 5,902,812 and 5,891,877).

Cancer

Current therapies for cancer are generally characterized by limited

efficacy, or significant and/or debilitating side effects. In certain solid tumor cancers, malignant tumors invade and disrupt nearby tissues and can also metastasize or spread to other organs and tissues. The impact of these secondary metastatic tumors on vital organs such as the lungs and the liver frequently leads to death. Surgery is used to remove solid tumors that are accessible to the surgeon and can be effective if the cancer has not metastasized. Radiation therapy also can be employed to irradiate a solid tumor and surrounding tissues and is a firstline therapy for inoperable tumors, but side effects are a limiting factor in treatment. Radiation therapy is used frequently in conjunction with surgery either to reduce the tumor mass prior to surgery or to destroy tumor cells that may remain at the tumor site after surgery. However, radiation therapy cannot assure that all tumor cells will be destroyed and has only limited utility for treating widespread metastases. While surgery and radiation therapy are the primary treatments for solid tumors, chemotherapy and hormonal treatments often are used as adjunctive therapies and also are used as primary therapies for inoperable or metastatic cancers. However, the side effects of these therapies can often limit their effectiveness due to patient tolerance and compliance.

Plasminogen activator inhibitor (PAI) and its role in solid tumor cancer

The role of PAI, particularly PAI-1, in the natural progression of certain solid tumor cancers has been suggested based on the strong correlation of increased levels of this protein and a poor patient survival rates in certain types of cancer, including breast cancer. In addition, recent evidence in animals genetically lacking PAI (PAI knockouts) has demonstrated that the growth and metastasis of certain human tumors is significantly impaired, suggesting that PAI may play a pivotal role in the growth and metastatic migration of certain solid tumors (Bajou et al. (1998) Nat. Med. 4(8):923-928).

PAI antagonists that have been reported to date include the anthranilic acid derivative AR-H029953XX (Björquist et al. (1998) Biochemistry 37:1227-1234) and several diketopiperazines (piperazinediones)(see, e.g., Charlton et al. (1997) Fibrinolysis & Proteolysis 11(1):51-56; Charlton et al. (1996) Thrombosis and Haemostasis 75(5):808-815; and U.S. Patent Nos. 5,750,530; 5,902,812; and 5,891,877). See also European Patent Application Publication No. EP 0 819 686. U.S. Patent No. 3,794,729 discloses compounds for inhibition of blood platelet aggregation. Hence PAI-1 is a target for development of pharmaceuticals. Therefore, it is an object herein to provide compositions and methods for antagonizing the effects of PAI, particularly PAI-1, are provided. It is also an object herein to provide methods of treating, preventing, or ameliorating one or more symptoms of disease states, including, but not limited to, disease states mediated by or in which PAI-1 is implicated. These disease states include unstable angina, thrombotic disorders, such as myocardial infarction, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, particularly solid tumors, that are modulated or otherwise affected by the activity of PAI, particularly PAI-1. A further object herein is to provide methods of attenuating tumor or other cancer metastasis. Finally, it is an object herein to provide methods of modulating the interaction of PAs, particularly tPA and uPA, with PAI, particularly PAI-1.

SUMMARY OF THE INVENTION

Compounds and compositions useful as plasminogen activator inhibitor (PAI) antagonists are provided. The compounds and compositions are useful in the treatment, prevention, or amelioration of one or more symptoms of thrombotic disorders, such as myocardial infarction, reocclusion following thrombolytic therapy, deep vein

thrombosis and disseminated intravascular coagulation, and cancer, particularly tumors, solid tumors, metastatic solid tumors and breast cancer. The compositions contain compounds that are active in assays that measure PAI-1 antagonist activity, such as an assay described herein. The compounds contain optionally substituted aryl and/or heteroaryl groups linked via various moieties, including but not limited to, ethers, thioethers, ketones, diketones and esters, and possess at least one acidic moiety, as defined herein, on one of the aryl or heteroaryl groups. An acidic group refers to a molecular fragment that is spatially and/or electronically capable of mimicking a carboxylic acid or that has acidic properties. As used herein, preferred acidic moieties include those that exist in anionic or salt form under physiological conditions. Among the preferred compounds are benzophenones, benzoate esters, benzyl ethers, sulfones and benzils.

In particular, provided herein are compounds and pharmaceutical compositions that contain therapeutically effective amounts of a compound of formula MX'_jJ, or pharmaceutically acceptable derivatives thereof, in a pharmaceutically acceptable carrier. In these embodiments, j is 0 or 1, and the formula MX'_jJ is intended to represent the formulae M-X'-J (when j is 1) or MJ (when j is 0). In the compounds, X' is a direct link or is any suitable linkage such that the resulting compound has activity as a PAI-1 antagonist, and as noted above, at least one of M and J possesses an acidic group.

In one embodiment, the compounds for use in the compositions and methods provided herein have formula (I): MX'_jJ, or a pharmaceutically acceptable derivative thereof, wherein M, X', j and J are selected from (i) or (ii) as follows:

(i) j is 1 and the compound has the formula M-X'-J;
X' is selected from (i) or (ii) as follows:

(i) X' is a direct link or is a divalent group having any combination of the following groups: arylene, heteroarylene excluding benzo[b]thienylene, cycloalkylene, $C(R^{15})_2$, $-C(R^{15})=C(R^{15})-$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{15})$, $P(D)_v(ER^{15})$, $N(R^{15})$, $>N^+(R^{23})(R^{24})$ and C(E); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{15}; D is S or O; and E is S, O or NR^{15}; which groups may be combined in any order; or

(ii) X' is a trivalent, tetravalent, pentavalent or hexavalent group having any combination of the following groups: arylene, heteroarylene, cycloalkylene, $C(R^{15})_2$, $-C(R^{15})=C(R^{15})-$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{15})$, $P(D)_v(GR^{15})$, $N(R^{15})$, $>N^+(R^{23})(R^{24})$, $C(R^{16})_2$, $C(R^{15})(R^{16})$, $-C(R^{16})=C(R^{15})-$, $-C(R^{16})=C(R^{16})-$, $S(NR^{16})$, $P(D)_v(R^{16})$, $P(D)_v(GR^{16})$, $N(R^{16})$ or C(G); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{15}; D is S or O; and G is S, O, NR^{15} or NR^{16}; which groups may be combined in any order, and forms one or more fused rings with M and/or J;

each R^{15} is a monovalent group independently selected from the group consisting of hydrogen and X^2-R^{18};

each X^2 is a divalent group independently having any combination of the following groups: a direct link, arylene, heteroarylene, cycloalkylene, $C(R^{17})_2$, $-C(R^{17})=C(R^{17})-$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{17})$, $P(D)_v(ER^{17})$, $N(R^{17})$, $N(COR^{17})$, $>N^+(R^{23})(R^{24})$ and C(E); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{17}; D is S or O; and E is S, O or NR^{17}; which groups may be combined in any order;

R^{17} and R^{18} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, nitro, $SiR^{27}R^{28}R^{25}$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl,

heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{19} and R^{20} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl and heterocyclyl;

h is 0, 1 or 2;

each R^{16} is a divalent group independently having any combination of the following groups: arylene, heteroarylene, cycloalkylene, $C(R^{17})_2$, $-C(R^{17})=C(R^{17})-$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{17})$, $P(D)_v(GR^{17})$, $N(R^{17})$, $N(COR^{17})$, $>N^+(R^{23})(R^{24})$, $C(R^{21})_2$, $C(R^{17})(R^{21})$, $-C(R^{21})=C(R^{17})-$, $-C(R^{21})=C(R^{17})-$, $S(NR^{21})$, $P(D)_v(R^{21})$, $P(D)_v(GR^{21})$, $N(R^{21})$, $N(COR^{21})$ or C(G); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{17}; D is S or O; and G is S, O, NR^{17} or NR^{21}; which groups may be combined in any order;

each R^{21} is a divalent group and each is independently selected from alkylene, alkenylene, alkynylene, arylene, heteroarylene, heterocyclylene, cycloalkylene, cycloalkenylene, alkylenoxy, arylenoxy, aralkylene, aralkenylene, aralkynylene, heteroaralkylene, heteroaralkenylene, heteroaralkynylene, aralkylenoxy, and heteroaralkylenoxy;

R^{23} and R^{24} are selected from (i) or (ii) as follows:

(i) R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

(ii) R^{23} and R^{24} together form alkylene, alkenylene or cycloalkylene;

M and J are each independently selected from (i) or (ii):

(i) monocyclic or polycyclic cycloalkyl, heterocyclyl, aryl,

heteroaryl, or two or more fused or bridged cycloalkyl, heterocyclyl, aryl or heteroaryl rings; or

(ii) one of M or J is alkyl, alkenyl, alkynyl, cycloalkyl, or heterocyclyl, and the other is selected as in (i);

with the proviso that at least one of M and J is substituted with at least one acidic group;

M and J are each independently unsubstituted or substituted with one or more substituents independently selected from R^{15};

M and J are optionally substituted with and bridged by one or more divalent groups selected from R^{16};

M and/or J are optionally substituted with and form a ring with one or more divalent groups selected from R^{16};

R^{25}, R^{27} and R^{28} are each independently a monovalent group selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{27} and R^{28} may be substituted with one or more substituents each independently selected from Z^2, wherein Z^2 is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy, $S(O)_hR^{35}$, $NR^{35}R^{36}$, $COOR^{35}$, COR^{35}, $CONR^{35}R^{36}$, $OC(O)NR^{35}R^{36}$, $N(R^{35})C(O)R^{36}$, alkoxy, aryloxy, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, aralkoxy, heteroaralkoxy, alkoxycarbonyl, carbamoyl, thiocarbamoyl, alkoxycarbonyl, carboxyaryl, halo, pseudohalo, haloalkyl and carboxamido;

R^{35} and R^{36} are each independently selected from among

hydrogen, halo, pseudohalo, cyano, azido, nitro, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy, amino, amido, alkylamino, dialkylamino, alkylarylamino, diarylamino and arylamino;

wherein, if X' is O or CH_2, the compound does not exhibit substantial thyroid hormone activity; and wherein the resulting compound has activity as a plasminogen activator inhibitor (PAI) antagonist; and wherein the resulting compound is chemically stable so that it can be formulated for pharmaceutical use; or

(ii) j is 0 and the compound has the formula MJ;

M and J together form a fused multicyclic, preferably a fused bicyclic, tricyclic or tetracyclic, ring system where M and J are each independently selected from cycloalkyl, heterocyclyl, aryl and heteroaryl, with the proviso that at least one of M and J is substituted with at least one acidic group;

M and J are each independently unsubstituted or substituted with one or more substituents independently selected from R^{15};

each R^{15} is independently selected as in (i), above;

wherein the resulting compound has activity as a plasminogen activator inhibitor (PAI) antagonist; and wherein the resulting compound is chemically stable so that it can be formulated for pharmaceutical use.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula (I): MX'_jJ, or a pharmaceutically acceptable derivative thereof, wherein M, X', j and J are

selected from (i) or (ii) as follows:

(i) j is 1 and the compound has the formula M-X'-J;

X' is selected from (i) or (ii) as follows:

(i) X' is a divalent group having any combination of the following groups: arylene, heteroarylene excluding benzo[b]thienylene, cycloalkylene, $C(R^{15})_2$, $-C(R^{15})=C(R^{15})-$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{15})$, $P(D)_v(ER^{15})$, $N(R^{15})$, $>N^+(R^{23})(R^{24})$ and C(E); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{15}; D is S or O; and E is S, O or NR^{15}; which groups may be combined in any order; or

(ii) X' is a trivalent, tetravalent, pentavalent or hexavalent group having any combination of the following groups: arylene, heteroarylene, cycloalkylene, $C(R^{15})_2$, $-C(R^{15})=C(R^{15})-$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{15})$, $P(D)_v(GR^{15})$, $N(R^{15})$, $>N^+(R^{23})(R^{24})$, $C(R^{16})_2$, $C(R^{15})(R^{16})$, $-C(R^{16})=C(R^{15})-$, $-C(R^{16})=C(R^{16})-$, $S(NR^{16})$, $P(D)_v(R^{16})$, $P(D)_v(GR^{16})$, $N(R^{16})$ or C(G); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{15}; D is S or O; and G is S, O, NR^{15} or NR^{16}; which groups may be combined in any order, and forms one or more fused rings with M and/or J;

each R^{15} is a monovalent group independently selected from the group consisting of hydrogen and X^2-R^{18};

each X^2 is a divalent group independently having any combination of the following groups: a direct link, arylene, heteroarylene, cycloalkylene, $C(R^{17})_2$, $-C(R^{17})=C(R^{17})-$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{17})$, $P(D)_v(ER^{17})$, $N(R^{17})$, $N(COR^{17})$, $>N^+(R^{23})(R^{24})$ and C(E); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{17}; D is S or O; and E is S, O or NR^{17}; which groups may be combined in any order;

R^{17} and R^{18} are each independently selected from the group

consisting of hydrogen, halo, pseudohalo, cyano, azido, nitro, $SiR^{27}R^{28}R^{25}$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{19} and R^{20} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl and heterocyclyl;

h is 0, 1 or 2;

each R^{16} is a divalent group independently having any combination of the following groups: arylene, heteroarylene, cycloalkylene, $C(R^{17})_2$, $-C(R^{17})=C(R^{17})-$, $-C\equiv C-$, O, $S(A)_u$, $P(D)_v(R^{17})$, $P(D)_v(GR^{17})$, $N(R^{17})$, $N(COR^{17})$, $>N^+(R^{23})(R^{24})$, $C(R^{21})_2$, $C(R^{17})(R^{21})$, $-C(R^{21})=C(R^{17})-$, $-C(R^{21})=C(R^{17})-$, $S(NR^{21})$, $P(D)_v(R^{21})$, $P(D)_v(GR^{21})$, $N(R^{21})$, $N(COR^{21})$ or C(G); where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{17}; D is S or O; and G is S, O, NR^{17} or NR^{21}; which groups may be combined in any order;

each R^{21} is a divalent group and each is independently selected from alkylene, alkenylene, alkynylene, arylene, heteroarylene, heterocyclylene, cycloalkylene, cycloalkenylene, alkylenoxy, arylenoxy, aralkylene, aralkenylene, aralkynylene, heteroaralkylene, heteroaralkenylene, heteroaralkynylene, aralkylenoxy, and heteroaralkylenoxy;

R^{23} and R^{24} are selected from (i) or (ii) as follows:

(i) R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

(ii) R^{23} and R^{24} together form alkylene, alkenylene or

cycloalkylene;

M and J are each independently selected from (i) or (ii):

(i) monocyclic or polycyclic cycloalkyl, heterocyclyl, aryl, heteroaryl, or two or more fused or bridged cycloalkyl, heterocyclyl, aryl or heteroaryl rings; or

(ii) one of M or J is alkyl, alkenyl, alkynyl, cycloalkyl, or heterocyclyl, and the other is selected as in (i);

with the proviso that at least one of M and J is substituted with at least one acidic group;

M and J are each independently unsubstituted or substituted with one or more substituents independently selected from R^{15};

M and J are optionally substituted with and bridged by one or more divalent groups selected from R^{16};

M and/or J are optionally substituted with and form a ring with one or more divalent groups selected from R^{16};

R^{25}, R^{27} and R^{28} are each independently a monovalent group selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{27} and R^{28} may be substituted with one or more substituents each independently selected from Z^2, wherein Z^2 is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy, $S(O)_hR^{35}$, $NR^{35}R^{36}$, $COOR^{35}$, COR^{35}, $CONR^{35}R^{36}$, $OC(O)NR^{35}R^{36}$, $N(R^{35})C(O)R^{36}$, alkoxy, aryloxy, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, aralkoxy, heteroaralkoxy, alkoxycarbonyl, carba-

moyl, thiocarbamoyl, alkoxycarbonyl, carboxyaryl, halo, pseudohalo, haloalkyl and carboxamido;

R^{35} and R^{36} are each independently selected from among hydrogen, halo, pseudohalo, cyano, azido, nitro, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy, amino, amido, alkylamino, dialkylamino, alkylarylamino, diarylamino and arylamino;

wherein, if X' is O or CH_2, the compound does not exhibit substantial thyroid hormone activity; and wherein the resulting compound has activity as a plasminogen activator inhibitor (PAI) antagonist; and wherein the resulting compound is chemically stable so that it can be formulated for pharmaceutical use; or

(ii) j is 0 and the compound has the formula MJ;

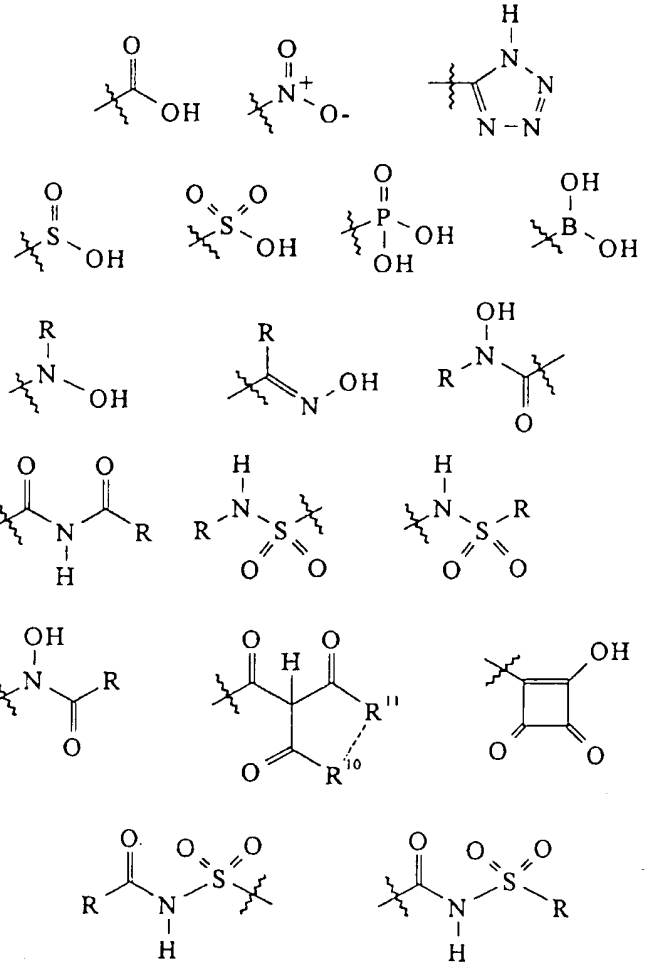
M and J together form a fused multicyclic, preferably a fused bicyclic, tricyclic or tetracyclic, ring system where M and J are each independently selected from cycloalkyl, heterocyclyl, aryl and heteroaryl, with the proviso that at least one of M and J is substituted with at least one acidic group;

M and J are each independently unsubstituted or substituted with one or more substituents independently selected from R^{15};

each R^{15} is independently selected as in (i), above;

wherein the resulting compound has activity as a plasminogen activator inhibitor (PAI) antagonist; and wherein the resulting compound is chemically stable so that it can be formulated for pharmaceutical use.

Exemplary acidic groups include, but are not limited to, phenolic groups, carboxylic acid, sulfonic acid, sulfinic acid, phosphonic acid, phosphinic acid and boronic acid groups. Thus, acidic and acid mimicking groups include, but are not limited to, the following:



or cyclic derivatives thereof, where R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl or heteroaralkyl; and R^{10} and R^{11} are each independently alkyl, aryl, alkoxy, haloalkyl, haloalkoxy, halo or pseudohalo.

The substituents R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}

and R^{25} are selected such that the resulting compound has PAI-1 antagonist activity, particularly in at least one assay described herein, and preferably at an IC_{50} of less than about 100 μM. Significantly, the compounds, which include thyroxine analogs, preferably do not exhibit thyroid hormone activity at a level that would detectably alter thyroid function, i.e., altering pulse, body temperature or weight, in a human given a dose of the compound. Thus, preferred compounds do not exhibit substantial thyroid hormone activity and must exhibit PAI-1 antagonist activity, preferably exhibiting an IC_{50} of at least about 100 μM in assays described herein.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, acids, enol ethers and esters, bases, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an

appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of thrombotic disorders, including, but not limited to, myocardial infarction, thrombosis associated with diabetes or obesity, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, including, but not limited to, tumors, solid tumors, metastatic solid tumors and breast cancer, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the disorders.

Methods for treatment, prevention, or amelioration of diseases mediated by or in which PAI-1 is implicated are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of thrombotic disorders, including, but not limited to, myocardial infarction, thrombosis associated with diabetes or obesity, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, including, but not limited to, tumors, solid tumors, metastatic solid tumors and breast cancer, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, are provided.

Methods of modulating the activity of PAI, particularly PAI-1, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays that measure the activity of PAI, specifically PAI-1. Preferred are methods of inhibiting the activity of PAI, in particular PAI-1. Preferred compounds are those that do not exhibit substantial thyroid hormone activity.

Methods of modulating the interaction of PAs, particularly tPA and uPA, with PAI, particularly PAI-1, by administering one or more of the

compounds provided herein, or pharmaceutically acceptable derivatives thereof, are provided.

Methods of attenuating metastasis by administration of one or more of the compounds and compositions provided herein are also provided.

Methods of modulating angiogenesis, preferably inhibiting angiogenesis, by administration of one or more of the compounds and compositions provided herein are provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds formulated for systemic, including parenteral, oral, and intravenous delivery, local or topical application for the treatment of PAI-1 mediated or disorders in which PAI-1 is implicated, including, but are not limited to, unstable angina, thrombotic disorders, including, but not limited to, myocardial infarction, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, including, but not limited to, tumors, solid tumors, metastatic solid tumors and breast cancer, are administered to an individual exhibiting the symptoms of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for antagonizing PAI, particularly PAI-1, or for treatment, prevention or amelioration of one or more symptoms of thrombotic disorders, including, but not limited to, myocardial infarction, thrombosis associated with diabetes or obesity, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, including, but not limited to,

tumors, solid tumors, metastatic solid tumors and breast cancer, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for antagonizing PAI, particularly PAI-1, or for treatment, prevention or amelioration of one or more symptoms of thrombotic disorders, including, but not limited to, myocardial infarction, thrombosis associated with diabetes or obesity, reocclusion following thrombolytic therapy, deep vein thrombosis and disseminated intravascular coagulation, and cancer, including, but not limited to, tumors, solid tumors, metastatic solid tumors and breast cancer, are provided.

DESCRIPTION OF THE FIGURES

FIGURES 1 and 2 set forth exemplary compounds for use in the compositions and methods provided herein, and their structures.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. For U.S. purposes and where appropriate, all patents, patent applications and publications referred to herein are incorporated by reference in their entirety.

As used herein, "plasmin" refers to the trypsin-like serine protease that is responsible for digesting fibrin in blood clots. Plasmin is generated from plasminogen by the action of another protease, plasminogen activator.

As used herein, "plasminogen" refers to the zymogen of plasmin.

As used herein, "plasminogen activator" or "PA" refers to a serine protease that acts on plasminogen to generate plasmin. PA is produced by many normal and invasive cells. Examples of PAs include, but are not limited to, uPA (urokinase, 70 kDa), tissue plasminogen activator (tPA,